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(54) Title: GAMMA-AMINOBUTYRIC ACID DERIVATIVES CONTAINING, SOLID COMPOSITIONS AND PROCESS FOR PREPARING THE SAME

(57) Abstract: The present invention provides a stabilized solid composition containing a 4-amino-3-substituted-butanoic acid

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GAMMA-AMINOBUTYRIC ACID DERIVATIVES CONTAINING, SOLID COMPOSITIONS AND
PROCESS FOR PREPARING THE SAME

FIELD OF THE INVENTION

5 This invention relates to a stabilized solid
composition comprising a 4-amino-3-substituted-butanoic acid
derivative and a process for the preparation of the same.

 Also, this invention relates to a solid
pharmaceutical preparation of the 4-amino-3-substituted-
10 butanoic acid derivative comprising the stabilize solid
composition and a process for the preparation of the same.

 More particularly, the invention is concerned with
a stabilized solid pharmaceutical preparation of the 4-
amino-3-substituted-butanoic acid derivative, including
15 gabapentin, pregabalin, baclofen, 3-aminomethyl-4-
cyclohexyl-butanoic acid, 3-aminomethyl-5-cyclohexyl
pentanoic acid, 3-aminomethyl-4-phenyl-butanoic acid or 3-
aminomethyl-5-phenyl-pentanoic acid, in the dosage forms of
tablets, powders, granules and capsules, as well as a process
20 for the preparation of the same.

BACKGROUND OF THE INVENTION

 1-(Aminomethyl)cyclohexanecetic acid, one of the
4-amino-3-substituted-butanoic acid derivatives, having the

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greatly increased utility of gabapentin as the therapeutic agents for those diseases or disorders or conditions as recited above, in addition to cerebral diseases such as epilepsy and the like.

5 As stated above, gabapentin is a very effective drug for cerebral diseases such as epilepsy and the like, and it has an extremely low toxicity. However, in order to maintain the effect as expected, it has been administered to adults usually at a single daily dose of 900 - 1800 mg or in
10 some cases a daily dose of up to 2400 mg in three divided doses. Thus, a single dose will be in the range of 300 - 600 mg or in some cases up to 800 mg.

 Further, gabapentin has difficulties in that it is a drug having a strongly bitter taste and also a very poor
15 fluidity and that an extremely high dosage should be required for administration in the dosage form of powders. Since gabapentin is very difficult to formulate because of its instability, gabapentin capsules now available in the
oversea markets are those manufactured by a simple dry
20 blending of gabapentin with necessary auxiliaries and subsequent encapsulating into hard capsules.

 However, a single dose is as high as 300 - 600 mg or in some cases up to 800 mg as stated above, which

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such auxiliaries with lapse of time would be further accelerated by the use of water or an organic solvent in manufacturing a pharmaceutical preparation.

It has been standardized in commercially available gabapentin capsules that an allowable content of the lactam up to the beyond-use date should be no more than 1.0% in view of safety. Accordingly, it is necessary in manufacturing a pharmaceutical preparation of gabapentin to prevent the formation of the lactam by retarding the dehydration reaction between the amino group and the carboxyl group within the molecule of gabapentin. On the other hand, there has been a demand for a small-sized dosage form for easier ingesting as discussed above. Under such circumstances, there have been attempted over years various methods. However, none of these attempts has succeeded either because a large-sized dosage form resulted due to a large amount of the auxiliaries used or because an increased amount of the lactam formed or both of them.

Such instability as encountered in manufacturing a gabapentin preparation has been also observed in other 4-amino-3-substituted-butanoic acid derivatives which are structurally analogous to gabapentin and have a structurally

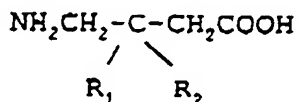
corresponding lactam form) by accelerating the dehydration reaction between the amino group and the carboxyl group within the molecule of the compound. This dehydration reaction would be far more accelerated as the compound is being more tightly compressed and would be further accelerated by the use of water or an organic solvent in manufacturing a pharmaceutical preparation, as is the case of gabapentin. It may be said that the mechanism of degradation by the autocondensation is peculiar to the 4-amino-3-substituted-butanoic acid derivatives having a structurally bulky substituent at the 3-position thereof.

To the contrary, in γ -aminobutyric acid derivatives having no or a less bulky substituent at the 3-position thereof, such as γ -aminobutyric acid or 4-amino-3-hydroxy-butanoic acid, the dehydration reaction is not brought about even when maintained in a dried state such as at a temperature of 105°C over 2 - 3 hours, and the formation of 4-cyclohexylpyrrolidone (the corresponding lactam form) is not observed. In other words, in the 4-amino-3-substituted-butanoic acid derivative wherein the substituent at the 3-position thereof has a bulky structure, the dehydration reaction could easily be brought about between the amino group and the carboxyl group within the molecule.

the 4-amino-3-substituted-butanoic acid derivative
stabilized by said humectant and a solid pharmaceutical
preparation using said composition such as tablets, granules
or the like have an excellent storage stability, on the
basis of which this invention has been completed.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a stabilized
solid composition containing a 4-amino-3-substituted-
butanoic acid derivative which comprises a 4-amino-3-
substituted-butanoic acid derivative having the general
formula



wherein,

R_1 is a hydrogen atom, a hydroxyl group, a methyl group or
an ethyl group;

R_2 is a monovalent group selected from:

a straight or branched alkyl group of 3 - 8 carbon
atoms;

a straight or branched alkylene group of 3-8 carbon
atoms;

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a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms wherein said phenyl ring is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group;

an alkylcycloalkyl group wherein said cycloalkyl has 3 - 8 carbon atoms and is linked to an alkylene group having 1 - 4 carbon atoms optionally interrupted with -O-, -S- or -SS-;

an alkylcycloalkyl group wherein said cycloalkyl has 3 - 8 carbon atoms, is linked to an alkylene group having 1 - 4 carbon atoms optionally interrupted with -O-, -S- or -SS- and is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a cycloalkyl group of 5 - 8 carbon atoms wherein one of the methylene groups (-CH₂-) is replaced by -O-, -NH-, -S-, -SO- or -S(O)₂-;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkyl group of 5 - 8 carbon atoms wherein one of the methylene groups ($-\text{CH}_2-$) is replaced by $-\text{O}-$, $-\text{NH}-$, $-\text{S}-$, $-\text{SO}-$ or $-\text{S}(\text{O})_2-$;

5 a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkyl group of 5 - 8 carbon atoms wherein one of the methylene groups ($-\text{CH}_2-$) is replaced by $-\text{O}-$, $-\text{NH}-$, $-\text{S}-$, $-\text{SO}-$ or $-\text{S}(\text{O})_2-$, said phenyl group being mono- or di-substituted with a halogen atom, a

10 trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms, one of the methylene groups ($-\text{CH}_2-$) in said cycloalkenyl ring or cycloalkanedienyl ring being replaced by $-\text{O}-$, $-\text{NH}-$, $=\text{N}-$, $-\text{S}-$, $-\text{SO}-$ or $-\text{S}(\text{O})_2-$;

15 a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms, one of the methylene groups ($-\text{CH}_2-$) in said cycloalkenyl ring or cycloalkanedienyl ring being replaced by $-\text{O}-$, $-\text{NH}-$, $=\text{N}-$, $-\text{S}-$,

20

a phenyl group substituted with a methylenedioxy group;

a phenyl or naphthyl group which is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an amino group, a nitro group, a carboxyl group, a phenoxy group, a phenylmethoxy group, a phenylmethoxy group wherein said phenyl ring is mono-substituted with a halogen atom, trifluoromethyl group, an alkoxy group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group, a cycloalkylmethoxy group having 5 - 8 carbon atoms in the cycloalkyl ring, a cycloalkenylmethoxy group having 5 - 8 carbon atoms in the cycloalkenyl ring, a cycloalkanedienylmethoxy group having 5 - 8 carbon atoms in the cycloalkanedienyl ring, a cycloalkylmethoxy group wherein one of the methylene groups (-CH₂-) in said cycloalkyl ring having 5 - 8 carbon atoms is replaced by -O-, -NH-, -S-, -SO- or -S(O)₂-, a cycloalkenylmethoxy group wherein one of the methylene groups (-CH₂-) in said cycloalkenyl ring having 5 - 8 carbon atoms is replaced by -O-, -NH-, =N-, -S-, -SO- or -S(O)₂-, a cycloalkanedienylmethoxy group wherein one of the methylene groups (-CH₂-) in said cycloalkanedienyl ring having 5 - 8 carbon atoms is

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replaced by -O-, -NH-, =N-, -S-, -SO- or -S(O)₂-;

an alkylphenyl group wherein said phenyl group is linked to an alkylene group having 1 - 4 carbon atoms optionally interrupted with -O-, -S- or -SS-;

5 an alkyl-O-, -S- or -SS-phenyl group wherein said phenyl group is linked to an alkylene group having 1 - 4 carbon atoms via -O-, -S- or -SS-;

an -O-, -S- or -SS-phenyl group;

a diphenylamino group;

10 an alkylphenyl group wherein said phenyl group is linked to an alkylene group having 1 - 4 carbon atoms optionally interrupted with -O-, -S- or -SS- and mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, a alkyl group, an alkoxy group, an amino group, a nitro group or a carboxyl group;

15 an alkyl-O-, -S- or -SS-phenyl group wherein said phenyl group is linked to an alkylene group having 1 - 4 carbon atoms via -O-, -S- or -SS- and mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an amino group, a nitro group or a carboxyl group;

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with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

5 a cycloalkenylidene group of 5 - 8 carbon atoms or a cycloalkanedienylidene group of 5 - 8 carbon atoms;

 a cycloalkenylidene group of 5 - 8 carbon atoms or a cycloalkanedienylidene group of 5 - 8 carbon atoms which is mono-, di-, tri- or tetra-substituted with a halogen atom, a
10 trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, a cycloalkyl group, a phenyl group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

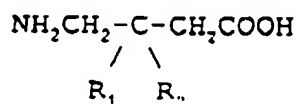
 a cycloalkenylidene group of 5 - 8 carbon atoms or a
15 cycloalkanedienylidene group of 5 - 8 carbon atoms wherein one of the methylene groups (-CH₂-) in said cycloalkenyl ring or cycloalkanedienyl ring is replaced by -O-, -NH-, =N-, -S-, -SO- or -S(O)₂-;

 a cycloalkenylidene group of 5 - 8 carbon atoms or a
20 cycloalkanedienylidene group of 5 - 8 carbon atoms wherein one of the methylene groups (-CH₂-) in said cycloalkenyl ring or cycloalkanedienyl ring is replaced by -O-, -NH-, =N-, -S-, -SO- or -S(O)₂- group and one or more of the unsubstituted

halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group; a humectant; and, if necessary, an auxiliary agent for manufacturing a pharmaceutical preparation.

The invention also relates to a solid composition containing a 4-amino-3-substituted-butanoic acid derivative which is a solid pharmaceutical preparation in the dosage form of tablets, powders, granules or capsules.

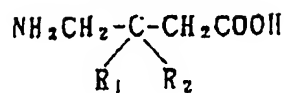
Also, the invention relates to a process for the preparation of a solid composition containing a 4-amino-3-substituted-butanoic acid derivative which comprises combining a 4-amino-3-substituted-butanoic acid derivative having the following formula



(wherein R_1 and R_2 are as defined above) with a humectant and, if necessary, an auxiliary agent for manufacturing a pharmaceutical preparation.

The invention further relates to a process for the preparation of a solid composition containing a 4-amino-3-substituted-butanoic acid derivative which is a solid

Table 1



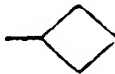
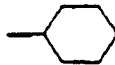

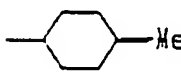
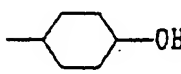
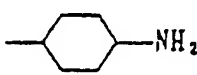
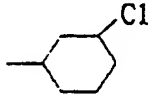
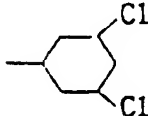
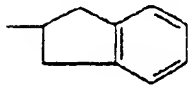
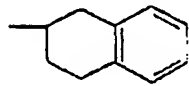

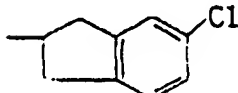
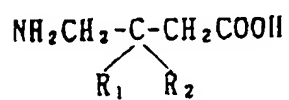
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-H	-CH(CH ₃) ₂		
-H	-CH ₂ -CH ₂ -CH ₂ -CH ₃	-H	
-H	-CH ₂ -CH(CH ₃) ₂		
-H	-C(CH ₂) ₃	-H	
-H	-(CH ₂) ₄ -CH ₃		
-H	-(CH ₂) ₅ -CH-(CH ₃) ₂	-H	
-H	-CH(CH ₂ -CH ₃)(CH ₃)		
-H	-CH ₂ -CH ₂ -CH ₂ NH ₂	-H	
-H	-CH ₂ -CH ₂ -CH ₂ -CH ₂ -NH ₂		
-H	-CH ₂ -CH ₂ -CH ₂ Cl	-H	
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-H	-CH ₂ -CH ₂ -CH ₂ Br		
-H	-CH ₂ -CH ₂ -CH ₂ I	-H	
-H	-CH ₂ -CH(CH ₃)-CHCl		
-H	-CH ₂ -CO-CH ₃	-H	
-H	-CH ₂ -CH ₂ -CO-CH ₃		
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Table 1 (Cont'd)



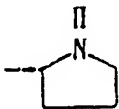
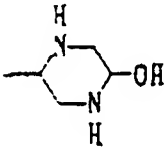
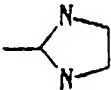

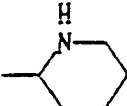
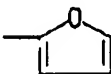
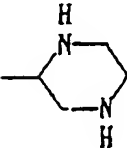
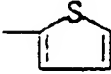
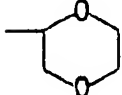
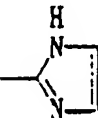
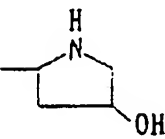
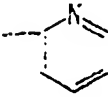
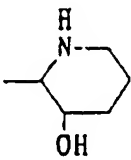
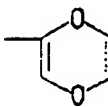
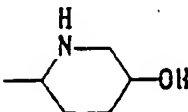
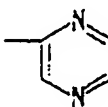

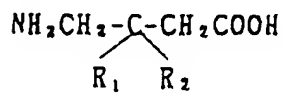
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Table 1 (Cont'd)

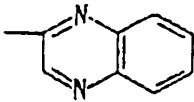
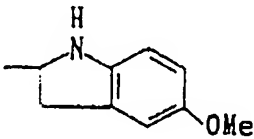
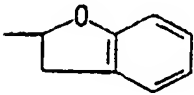
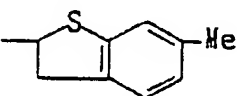
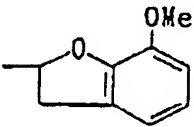
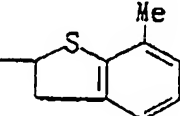
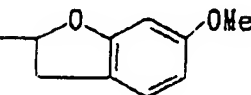
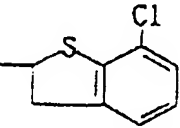
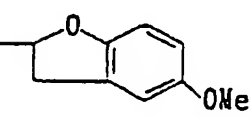
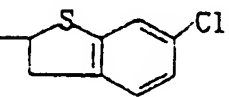
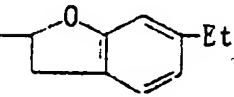
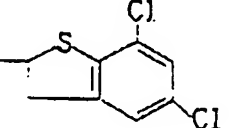
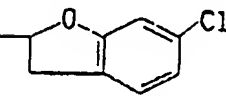
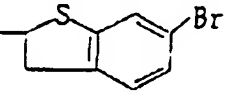
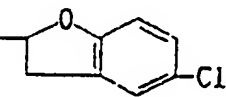
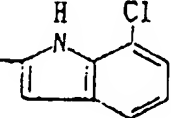
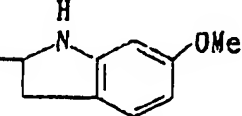
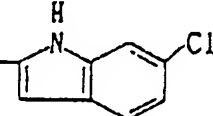
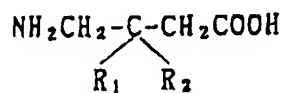
<u>-R₁</u>	<u>-R₂</u>	<u>-R₁</u>	<u>-R₂</u>
-H		-H	
-H		-H	
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-H		-H	
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-H		-H	

Table 1 (Cont'd)



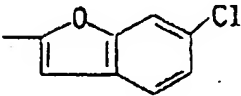
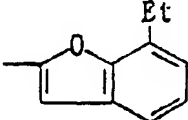
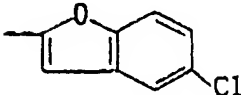
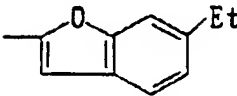
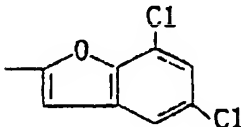
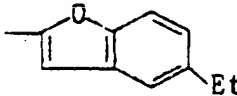
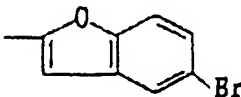
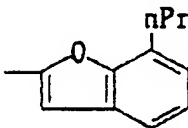
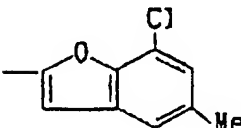
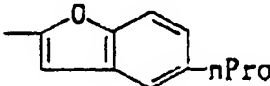
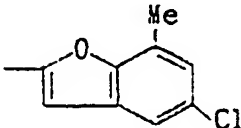
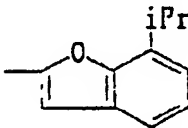
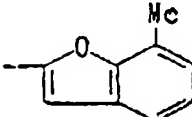
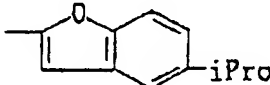
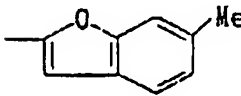
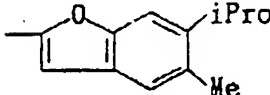
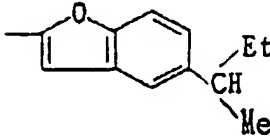
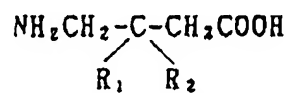
<u>-R₁</u>	<u>-R₂</u>	<u>-R₁</u>	<u>-R₂</u>
-H		-H	
-H		-H	
-H		-H	
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-H		-H	

Table 1 (Cont'd)



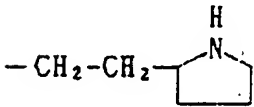
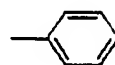
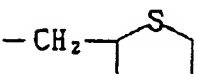
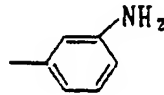
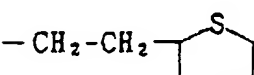
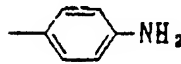
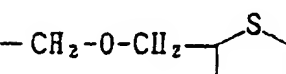

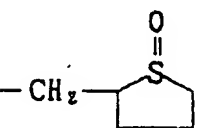
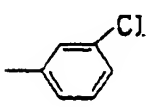
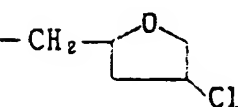
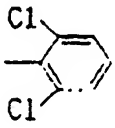
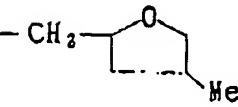
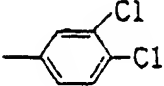
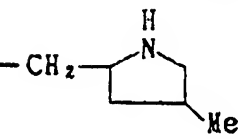
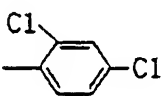
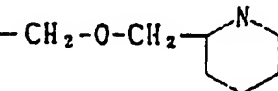

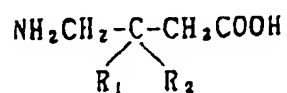
<u>-R₁</u>	<u>-R₂</u>	<u>-R₁</u>	<u>-R₂</u>
-H		-H	
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-H		-H	
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-H		-H	

Table 1 (Cont'd)



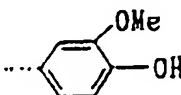
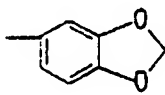
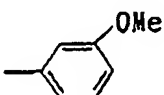
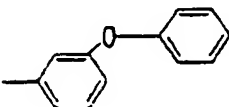
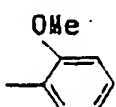
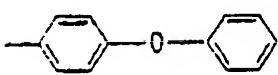
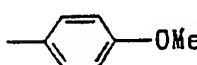
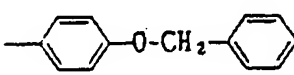
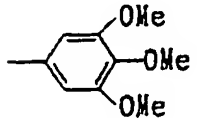
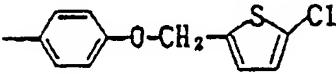
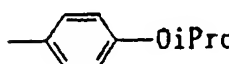
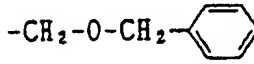
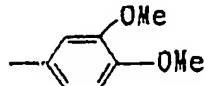
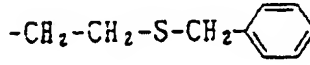
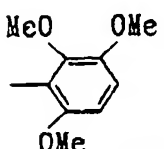
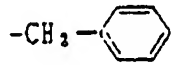
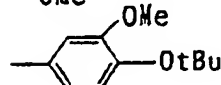
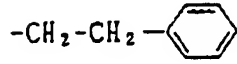
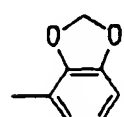
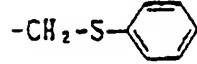
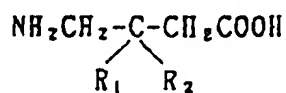
<u>-R₁</u>	<u>-R₂</u>	<u>-R₁</u>	<u>-R₂</u>
-H		-H	
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-H		-H	

Table 1 (Cont'd)



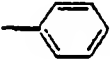
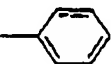
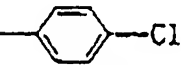
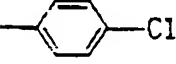
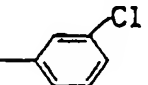

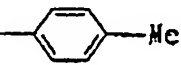


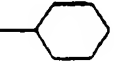
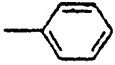
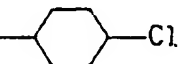
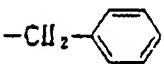
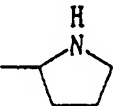

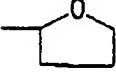
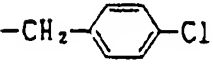
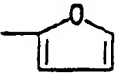

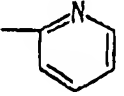
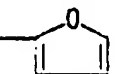
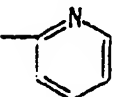
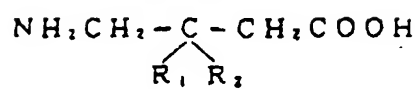

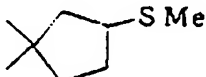

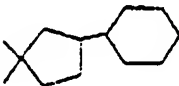

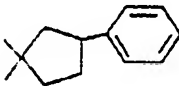
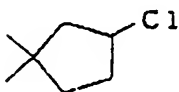
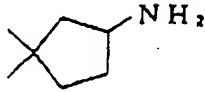
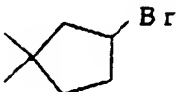
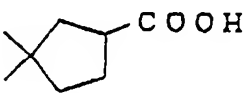
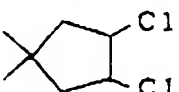
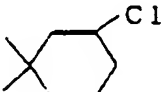
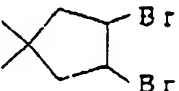
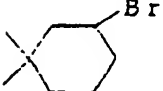
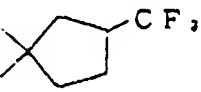

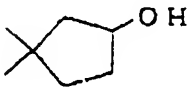
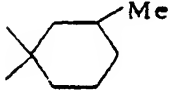
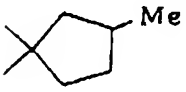
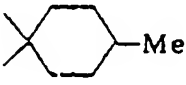
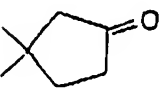
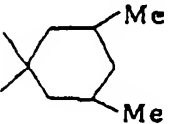
<u>-R₁</u>	<u>-R₂</u>	<u>-R₁</u>	<u>-R₂</u>
-OH	-CH ₂ -C(CH ₃) ₃	-CH ₃	-CH(CH ₃) ₂
-OH	-CH ₂ -CH ₂ -CH ₃	-CH ₃	-CH ₂ -CH(CH ₃) ₂
-OH	-CH ₂ -CH ₂ -CH ₂ -CH ₃	-CH ₃	-CH ₂ -CH ₂ -CH ₂ -CH ₃
-OH	-CH ₂ -CH(CH ₃) ₂		
		-CH ₃	
-OH			
-OH		-CH ₃	
-OH		-CH ₃	-CH ₂ - 
-OH		-CH ₃	-CH ₂ - 
-OH	-CH ₂ -O- 	-CH ₂ -CH ₃	-CH ₂ -CH(CH ₃) ₂
-OH		-CH ₃	
-OH		-CH ₂ -CH ₃	-CH ₂ - 
-OH		-CH ₂ -CH ₃	
-OH		-CH ₂ -CH ₃	-CH ₂ - 
-OH		-CH ₂ -CH ₃	
-OH		-CH ₂ -CH ₃	
-CH ₃	-CH ₂ -CH ₂ -CH ₃		

Table 2



$\text{>C}<\begin{smallmatrix} \text{R}_1 \\ \text{R}_2 \end{smallmatrix}$	$\text{>C}<\begin{smallmatrix} \text{R}_1 \\ \text{R}_2 \end{smallmatrix}$
	
	
	
	
	
	
	
	
	
	
	

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solid preparation of the 4-amino-3-substituted-butanoic acid derivative thus prepared, for example, in case of the gabapentin preparation, gabapentin is in a compressed or fluidized state so that the solid preparation may be easily taken when orally administered to human.

This invention will be more fully explained by way of the following examples, but it should not be construed that these examples limit the scope of this invention.

Example 1

1) Preparation of granular powders A of gabapentin

On 250 g of bulk powders of gabapentin was sprayed 72 g of water by means of a fluidized granulator (manufactured by FREUND Co., Ltd., SFC-Labo) and then dried to obtain gabapentin granular powders A.

2) Preparation of granular powders B of gabapentin

On 250 g of bulk powders of gabapentin was sprayed a solution of 5 g of propylene glycol in 67 g of water by means of said fluidized granulator and then dried to obtain gabapentin granular powders B.

The gabapentin granular powders A and B obtained as described in the above 1) and 2) were stored under the conditions as defined in the following Table 3 and then a

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subsequently a solution of 5 g of hydroxypropylcellulose in 58 g of water was sprayed thereon, and then dried to obtain gabapentin granular powders C.

2) Preparation of granular powders D of gabapentin

5 On 250 g of bulk powders of gabapentin was sprayed a solution of 5 g of propylene glycol in 67 g of water by means of a fluidized granulator (manufactured by FREUND Co., Ltd., SFC-Labo) and subsequently a solution of 5 g of hydroxypropylcellulose in 58 g of water was sprayed thereon, and then dried to obtain gabapentin granular powders D.

3) Preparation of granular powders E of gabapentin

10 On 250 g of bulk powders of gabapentin was sprayed a solution of 5 g of triacetin in 67 g of water by means of said fluidized granulator and subsequently a solution of 5 g of hydroxypropylcellulose in 58 g of water was sprayed thereon, and then dried to obtain gabapentin granular powders E.

4) Preparation of granular powders F of gabapentin

20 On 250 g of bulk powders of gabapentin was sprayed a solution of 2.5 g of propylene glycol and 2.5 g of triacetin in 67 g of water by means of the said fluidized granulator and subsequently a solution of 5 g of hydroxypropylcellulose in 58 g of water was sprayed thereon,

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glycol in 252 g of water by means of a fluidized granulator (manufactured by FREUND Co., Ltd., SFC-Mini) and then dried to obtain gabapentin granular powders.

2) Compression to tablets

5 The dry granules obtained according to the above step 1) were admixed with L-valine at 7% by weight based on the granules and then compressed to tablets, each tablet having a diameter of 9 mm and a weight of 336 mg, by means of a rotary tablet machine (manufactured by KIKUSUI
10 SEISAKUSHO K.K.). Each tablet contained 300 mg of gabapentin and had a hardness of 6 - 10 kg.

3) Surface coating of tablets

15 Tablets obtained in the above step 2) were film coated over the surface thereof with a coating solution having the composition as defined in the following Table 5 by means of a coater (manufactured by FREUND Co., Ltd., HI-COATOR HCT-30).

Table 5

	Copolyvidone	34.0 g
20	L-Isoleucine	13.5 g
	Glycine	13.5 g
	Propylene glycol	7.0 g
	Calcium stearate	7.0 g

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Moreover, the film coated tablets obtained as described above were subjected to the dissolution test according to the dissolution test procedure as prescribed in the Japanese Pharmacopoeia XIII (using 900 ml of water and a puddle method at 50 rpm). The test conditions and test results are shown in the following Table 7 wherein the numerical value means to represent the dissolution amount expressed in terms of %.

Table 7

Dissolution time (min.)	Storage conditions	
	When initiated	60°C/4 hrs (sealed)
15	90.3	91.5
30	103.1	103.3
60	103.2	103.3

The above test results have proved that the film coated gabapentin tablets prepared according to the process of this invention can exhibit a good dissolution in the dissolution test and also have a good stability with lapse of time after dissolution.

Example 4

1) Preparation of baclofen powder sample G

The above table shows that the granulated baclofen using water underwent an accelerated degradation with lapse of time (condensation with dehydration), and that the degradation with lapse of time could be prevented by the addition of propylene glycol as a humectant.

Example 5

1) Preparation of pregabalin powder sample I

1 g of pregabalin crystals was wetted with 0.1 ml of water and the mixture was made to granular powders by means of a mortar and then dried to obtain pregabalin powder sample I.

2) Preparation of pregabalin powder sample J

1 g of pregabalin crystals was wetted with 0.1 ml of a 1% aqueous solution of decaglyceryl monolaurate and the mixture was made to granular powders by means of a mortar and then dried to obtain pregabalin powder sample J.

3) Preparation of pregabalin powder sample K

1 g of pregabalin crystals was wetted with 0.1 ml of a 10% aqueous solution of butylene glycol and the mixture was made to granular powders by means of a mortar and then dried to obtain pregabalin powder sample K.

The samples I, J and K obtained as described above and untreated pregabalin crystals were stored under the

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mixture was made to granular powders by means of a mortar and then dried to obtain pregabalin powder sample L.

2) Preparation of pregabalin powder sample M

1 g of pregabalin crystals was wetted with 0.1 ml of an aqueous solution containing 10% hydroxypropylcellulose and 10% propylene glycol, and the mixture was made to granular powders by means of a mortar and then dried to obtain pregabalin powder sample M.

The samples L and M obtained as described above were stored under the conditions as defined in the following Table 10 and then a content of the dehydrated condensate formed in each of the samples was determined by means of HPLC.

Table 10

Storage conditions	Samples	
	L	M
When initiated	<0.001	<0.001
60°C/1 week (sealed)	0.005	0.001
60°C/2 weeks (sealed)	0.010	0.002
60°C/4 weeks (sealed)	0.014	0.004

The above table shows that the degradation with lapse of time (condensation with dehydration) of the pregabalin could be prevented by the addition of

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invention can be expected to greatly contribute to the development of a stabilized pharmaceutical composition containing the 4-amino-3-substituted-butanoic acid derivative.

a cycloalkyl group of 3 - 8 carbon atoms which is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkyl group of 4 - 8 carbon atoms;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkyl group of 4 - 8 carbon atoms wherein said phenyl ring is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms wherein said phenyl ring is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an

group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

5 a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms, one of the methylene groups (-CH₂-) in said cycloalkenyl ring or cycloalkanedienyl ring being replaced by -O-, -NH-, =N-, -S-, -SO- or -S(O)₂-;

10 a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms, one of the methylene groups (-CH₂-) in said cycloalkenyl ring or cycloalkanedienyl ring being replaced by -O-, -NH-, =N-, -S-, -SO- or -S(O)₂-, and one or two of the unsubstituted methylene groups (-CH₂-) being mono- or di-substituted with a
15 halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

20 a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkyl group of 5 - 8 carbon atoms wherein one of the methylene groups (-CH₂-) is replaced by -O-, -NH-, -S-, -SO- or -S(O)₂-;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkyl group of 5 - 8 carbon atoms

an alkylcycloalkyl group wherein said cycloalkyl has
5 - 8 carbon atoms and is linked to an alkylene group having
1 - 4 carbon atoms optionally interrupted with -O-, -S- or
-SS-, one of the methylene groups (-CH₂-) in said cycloalkyl
5 ring being replaced by -O-, -NH-, -S-, -SO- or -S(O)₂-;

an alkylcycloalkyl group wherein said cycloalkyl has
5 - 8 carbon atoms and is linked to an alkylene group having
1 - 4 carbon atoms optionally interrupted with -O-, -S- or
-SS-, and one of the methylene groups (-CH₂-) in said
10 cycloalkyl ring being replaced by -O-, -NH-, -S-, -SO- or
-S(O)₂- and one or two of the unsubstituted methylene groups
(-CH₂-) being mono-, di- or tri-substituted with a halogen
atom, a trifluoromethyl group, a hydroxyl group, an alkyl
group, an alkoxy group, an alkylthio group, an amino group,
15 a nitro group, an oxo group, a carboxyl group or a
carboalkoxy group;

a phenyl or naphthyl group;

a phenyl group substituted with a methylenedioxy
group;

20 a phenyl or naphthyl group which is mono-, di- or
tri-substituted with a halogen atom, a trifluoromethyl
group, a hydroxyl group, an alkyl group, an alkoxy group, an
amino group, a nitro group, a carboxyl group, a phenoxy

group and one of the methylene groups (-CH₂-) in said cycloalkyl ring is replaced by -O-, -NH-, -S-, -SO- or -S(O)₂-, a cycloalkenylmethoxy group having 5 - 8 carbon atoms in the cycloalkenyl ring wherein said cycloalkenyl ring is mono-substituted with a halogen atom, a trifluoromethyl group, a hydroxy group, an alkyl group, an alkoxy group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group and one of the methylene groups (-CH₂-) in said cycloalkenyl ring is replaced by -O-, -NH-, =N-, -S-, -SO- or -S(O)₂-, or a cycloalkanediethylmethoxy group having 5 - 8 carbon atoms in the cycloalkanediethyl ring wherein said cycloalkanediethyl ring is mono-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group and one of the methylene groups (-CH₂-) in said cycloalkanediethyl ring is replaced by -O-, -NH-, =N-, -S-, -SO- or -S(O)₂-;

an alkylphenyl group wherein said phenyl group is linked to an alkylene group having 1 - 4 carbon atoms optionally interrupted with -O-, -S- or -SS-;

or

R₁ and R₂, together with the carbon atom to which they are attached, may form a divalent group selected from:

a cycloalkylidene group of 5 - 8 carbon atoms;

5 a cycloalkylidene group of 5 - 8 carbon atoms which is mono-, di-, tri- or tetra-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, a cycloalkyl group, a phenyl group, an amino group, a nitro group or a
10 carboxyl group;

a cycloalkylidene group of 5 - 8 carbon atoms wherein one of the methylene groups (-CH₂-) in said cycloalkyl ring is replaced by -O-, -NH-, -S-, -SO- or -S(O)₂-;

15 a cycloalkylidene group of 5 - 8 carbon atoms wherein one of the methylene groups (-CH₂-) in said cycloalkyl ring is replaced by -O-, -NH-, -S-, -SO- or -S(O)₂- group and one or more of the unsubstituted methylene groups (-CH₂-) in said cycloalkyl ring are mono-, di-, tri- or tetra-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl
20 group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

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alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkylidene group of 4 - 8 carbon atoms;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkylidene group of 4 - 8 carbon atoms, said phenyl ring being mono-, di-, tri- or tetra-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenylidene group of 5 - 8 carbon atoms or a cycloalkanedienylidene group of 5 - 8 carbon atoms;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenylidene group of 5 - 8 carbon atoms or a cycloalkanedienylidene group of 5 - 8 carbon atoms, said phenyl ring being mono- or di-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group;

7. The stabilized solid composition containing a 4-amino-3-substituted-butanoic acid derivative as claimed in claim 1 wherein said humectant is sorbitol.

8. The stabilized solid composition containing a 4-amino-3-substituted-butanoic acid derivative as claimed in claim 1 wherein a total amount of said humectant is 0.01 - 25% by weight relative to the 4-amino-3-substituted-butanoic acid derivative.

9. The stabilized solid composition containing a 4-amino-3-substituted-butanoic acid derivative as claimed in claim 1 wherein a total amount of said humectant is 0.01 - 25% by weight relative to a total amount of the 4-amino-3-substituted-butanoic acid derivative and an auxiliary agent for manufacturing a pharmaceutical preparation.

10. The stabilized solid composition containing a 4-amino-3-substituted-butanoic acid derivative as claimed in claim 1 wherein it is a solid pharmaceutical preparation of gabapentin, pregabalin, baclofen, 3-aminomethyl-4-cyclohexyl-butanoic acid, 3-aminomethyl-5-cyclohexyl pentanoic acid, 3-aminomethyl-4-phenyl-butanoic acid or 3-aminomethyl-5-phenyl-pentanoic acid.

a cycloalkyl group of 3 - 8 carbon atoms which is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkyl group of 4 - 8 carbon atoms;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkyl group of 4 - 8 carbon atoms wherein said phenyl ring is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms wherein said phenyl ring is mono-, di- or tri-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an

group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

5 a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms, one of the methylene groups (-CH₂-) in said cycloalkenyl ring or cycloalkanedienyl ring being replaced by -O-, -NH-, =N-, -S-, -SO- or -S(O)₂-;

10 a cycloalkenyl group of 5 - 8 carbon atoms or a cycloalkanedienyl group of 5 - 8 carbon atoms, one of the methylene groups (-CH₂-) in said cycloalkenyl ring or cycloalkanedienyl ring being replaced by -O-, -NH-, =N-, -S-, -SO- or -S(O)₂-, and one or two of the unsubstituted methylene groups (-CH₂-) being mono- or di-substituted with a
15 halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

20 a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkyl group of 5 - 8 carbon atoms wherein one of the methylene groups (-CH₂-) is replaced by -O-, -NH-, -S-, -SO- or -S(O)₂-;

a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkyl group of 5 - 8 carbon atoms

an alkylcycloalkyl group wherein said cycloalkyl has
5 - 8 carbon atoms and is linked to an alkylene group having
1 - 4 carbon atoms optionally interrupted with -O-, -S- or
-SS-, one of the methylene groups (-CH₂-) in said cycloalkyl
5 ring being replaced by -O-, -NH-, -S-, -SO- or -S(O)₂-;

an alkylcycloalkyl group wherein said cycloalkyl has
5 - 8 carbon atoms and is linked to an alkylene group having
1 - 4 carbon atoms optionally interrupted with -O-, -S- or
-SS-, and one of the methylene groups (-CH₂-) in said
10 cycloalkyl ring being replaced by -O-, -NH-, -S-, -SO- or
-S(O)₂- and one or two of the unsubstituted methylene groups
(-CH₂-) being mono-, di- or tri-substituted with a halogen
atom, a trifluoromethyl group, a hydroxyl group, an alkyl
group, an alkoxy group, an alkylthio group, an amino group,
15 a nitro group, an oxo group, a carboxyl group or a
carboalkoxy group;

a phenyl or naphthyl group;

a phenyl group substituted with a methylenedioxy
group;

20 a phenyl or naphthyl group which is mono-, di- or
tri-substituted with a halogen atom, a trifluoromethyl
group, a hydroxyl group, an alkyl group, an alkoxy group, an
amino group, a nitro group, a carboxyl group, a phenoxy

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group and one of the methylene groups (-CH₂-) in said cycloalkyl ring is replaced by -O-, -NH-, -S-, -SO- or -S(O)₂-, a cycloalkenylmethoxy group having 5 - 8 carbon atoms in the cycloalkenyl ring wherein said cycloalkenyl ring is mono-substituted with a halogen atom, a trifluoromethyl group, a hydroxy group, an alkyl group, an alkoxy group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group and one of the methylene groups (-CH₂-) in said cycloalkenyl ring is replaced by -O-, -NH-, =N-, -S-, -SO- or -S(O)₂-, or a cycloalkanedienylmethoxy group having 5 - 8 carbon atoms in the cycloalkanedienyl ring wherein said cycloalkanedienyl ring is mono-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group and one of the methylene groups (-CH₂-) in said cycloalkanedienyl ring is replaced by -O-, -NH-, =N-, -S-, -SO- or -S(O)₂-;

an alkylphenyl group wherein said phenyl group is linked to an alkylene group having 1 - 4 carbon atoms optionally interrupted with -O-, -S- or -SS-;

or

R₁ and R₂, together with the carbon atom to which they are attached, may form a divalent group selected from:

a cycloalkylidene group of 5 - 8 carbon atoms;

5 a cycloalkylidene group of 5 - 8 carbon atoms which is mono-, di-, tri- or tetra-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, a cycloalkyl group, a phenyl group, an amino group, a nitro group or a
10 carboxyl group;

a cycloalkylidene group of 5 - 8 carbon atoms wherein one of the methylene groups (-CH₂-) in said cycloalkyl ring is replaced by -O-, -NH-, -S-, -SO- or -S(O)₂-;

15 a cycloalkylidene group of 5 - 8 carbon atoms wherein one of the methylene groups (-CH₂-) in said cycloalkyl ring is replaced by -O-, -NH-, -S-, -SO- or -S(O)₂- group and one or more of the unsubstituted methylene groups (-CH₂-) in said cycloalkyl ring are mono-, di-, tri- or tetra-substituted
20 with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

alkylthio group, an amino group, a nitro group, an oxo group, a carboxyl group or a carboalkoxy group;

5 a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkylidene group of 4 - 8 carbon atoms;

10 a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkylidene group of 4 - 8 carbon atoms, said phenyl ring being mono-, di-, tri- or tetra-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group;

15 a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenylidene group of 5 - 8 carbon atoms or a cycloalkanedienylidene group of 5 - 8 carbon atoms;

20 a condensed ring group formed by ortho-fusion of a phenyl ring with a cycloalkenylidene group of 5 - 8 carbon atoms or a cycloalkanedienylidene group of 5 - 8 carbon atoms, said phenyl ring being mono- or di-substituted with a halogen atom, a trifluoromethyl group, a hydroxyl group, an alkyl group, an alkoxy group, an alkylthio group, an amino group, a nitro group, a carboxyl group or a carboalkoxy group, which comprises combining the 4-amino-3-substituted-

17. The stabilized solid composition containing a 4-amino-3-substituted-butanoic acid derivative as claimed in claim 16 wherein said neutral amino acid is one or more of the neutral amino acids selected from L-leucine, L-isoleucine, L-valine, L-alanine, D-leucine, D-isoleucine, D-valine, D-alanine, DL-leucine, DL-isoleucine, DL-valine, DL-alanine and glycine.
- 5

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/10186

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 084 478 A (TUCKER HOWARD ET AL) 28 January 1992 (1992-01-28) the whole document ---	1,2, 10-15
A	EP 0 376 891 A (CIBA GEIGY AG) 4 July 1990 (1990-07-04) ---	
A	US 4 126 684 A (ROBSON RONALD D ET AL) 21 November 1978 (1978-11-21) -----	

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 99 /0186

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-9,12,13,16,17 relate to an extremely large number of possible compounds/products. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/products claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds/products, i.e.

Galenical compositions, which

a) comprise at least one of the exemplified actives
(gabapentin, baclofen, pregabalin)

and

b) comprise (at least one of the) specifically disclosed
disclosed humectants
and/or

feature a composition aimed at solving the underlying
problem of essentially
suppressing lactamisation of the active (during storage) by
proper selection
of the adjuvants:

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/10186

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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28-12-1977
